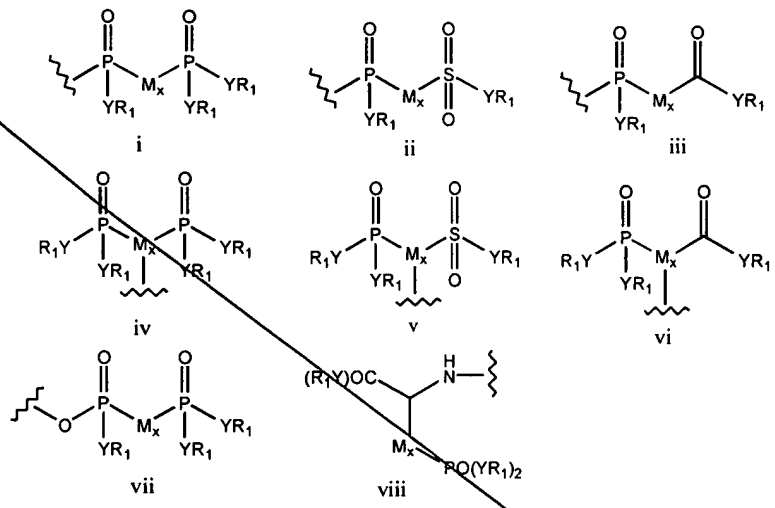
contd. A9



Sub C20

wherein each occurrence of M is independently CH_2, CHV, CHOH, or CV_2; each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl; wherein V is a halogen; each occurrence of x is independently 1-6, and in certain embodiments is 1 or 2; and each occurrence of R_1 is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, a prodrug or pharmaceutically acceptable derivative; and

wherein m is 1-3.

B) Marked-up Copies of Paragraphs and Claims:

1) Marked-up copy of amended paragraph for the paragraph on page 1, starting on line 3 and ending on line 13:

Priority Information

The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application number 60/172,510, filed December 17, 1999, entitled "Bone Targeting Agents", U.S. Provisional Patent Application number 60/172,161, filed December 17, 1999, entitled "Proton Pump Inhibitors", and U.S. Provisional Patent Application number 60/240,788, filed October 16, 2000 entitled "Bone Targeting Agents", and the entire contents of each of these applications are hereby incorporated by reference.

The application further claims priority to U.S. National Patent Application number [_____,] 09/740,267, entitled "Novel Heterocycles", and U.S. National Patent Application number [_____,] 09/740,619, entitled "Proton Pump Inhibitors", each of which is filed on even date herewith and is hereby incorporated by reference.

2) Marked-up copy of amended paragraph for paragraph on page 6, beginning on line 10 and ending on line 17:

wherein each occurrence of M is independently CH_2, CHV, CHOH, or CV_2; each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl; wherein V is a halogen; each occurrence of x is independently 1-6, and in certain embodiments is 1 or 2; and each occurrence of R_1 is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, a prodrug or pharmaceutically acceptable derivative; and wherein [M] m is 1-3.

3) Marked-up copy of amended paragraph for paragraph on page 15, beginning on line 19 and ending on line 30:

"Phosphorus containing moiety" As used herein, the phrase, "phosphorus containing moiety" includes, but is not limited to, phosphonates, bisphosphonates, phosphonic acids, bisphosphonic acids, phosphonic acid amides, tri-substituted phosphines, phosphinoxides, phosphonothionates, phosphoric acids, esters of phosphoric acids to name a few, and substituted versions thereof, to name a few. In certain embodiments of the invention, phosphorus containing moieties include, but are not limited to, phosphorous moieties having the structure -[P(O)YR_GYR_H,] P(X)YR_GYR_H, wherein X is independently an alkyl moiety, =O, =S; R_G and R_H, for each occurrence, are independently hydrogen, or substituted or unsubstituted aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, and each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

4) Marked-up copy of amended paragraph starting on page 25, line 20, and ending on page 26, line 19:

Other compounds of special interest include those compounds having the general structure:

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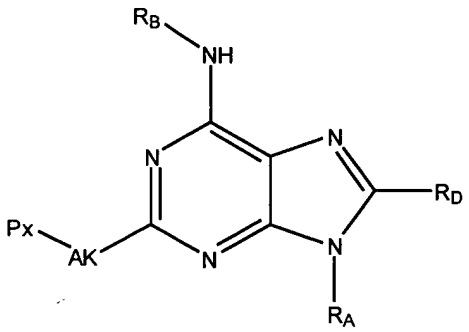

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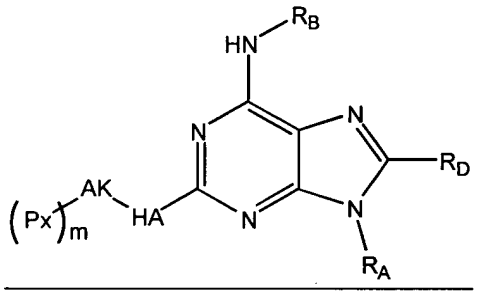

wherein R_A is hydrogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; R_B is an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; and R_D is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-ZR_E$, wherein Z is -O-, -S-, or NR_F, wherein R_E is hydrogen, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and R_F is an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein in each of the foregoing groups each aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl moiety may be branched or unbranched, cyclic or acyclic and substituted or unsubstituted, and each aryl and heteroaryl moiety may be substituted or unsubstituted;

wherein AK is a linear or branched, cyclic or acyclic, substituted or unsubstituted aliphatic or heteroaliphatic moiety[.] ; and

wherein HA is absent, -O-, -S- or –NH-;

5) Marked-up copy of amended paragraph starting on page 30, line 30 and ending on page 30, line 35:

It will be appreciated that the inventive compounds as described above and herein can be prepared using a variety of synthetic techniques known in the art, and as described herein. [. **(we'll also incorporate the three ariad published pcts by reference herein)**] In certain embodiments, combinatorial methods, either solution phase or solid phase are utilized, as described generally below and in more detail in the Exemplification section.

6) Marked-up copy of amended paragraph starting on page 116, line 9, and ending on page 117, line 5:

For example, compounds in which R_B is a moiety having the structure:

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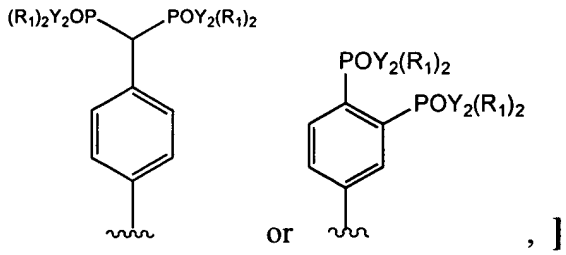

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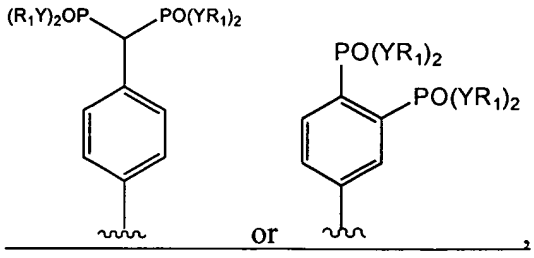
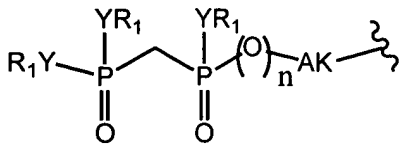
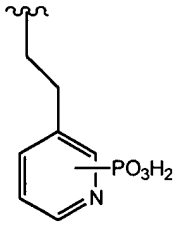


,

and those in which R_C is an amino moiety substituted with a group having the general structure:



wherein Y and R_1 are as defined herein, and AK is absent or is a linear or branched aliphatic moiety, wherein n is 0 or 1, and wherein R_A is an linear or branched, cyclic or acyclic aliphatic moiety, or is an aryl or alkylaryl moiety optionally substituted with one or more hydroxyl moieties, and wherein R_B is an aryl or heteroaryl moiety optionally substituted with one or more halogen atoms, as well as those in which R_C is -NH- substituted with a moiety having the structure:



have shown activities within these ranges.

7) Marked-up copy of amended claim 129:

129. The compound of claim [7aa] 125, wherein the aryl moiety is further substituted with 0-3 substituents selected from the group consisting of halogen, lower alkyl, lower alkenyl, aryl, heteroaryl, carbonyl, thiocarbonyl, ketone, aldehyde, amino, acylamino, amido, amidino, cyano, nitro, azido, sulfonyl, sulfoxido, sulfate, sulfonate, sulfamoyl, sulfonamido, phosphoryl, phosphorothioate, phosphonate, phosphinate, $-(CH_2)_p$alkyl, $-(CH_2)_p$alkenyl, $-(CH_2)_p$alkynyl, $-(CH_2)_p$aryl, $-(CH_2)_p$aralkyl, $-(CH_2)_p$OH, $-(CH_2)_p$O-lower alkyl, $-(CH_2)_p$O-lower alkenyl, $-O(CH_2)_nR$, $-(CH_2)_p$SH, $-(CH_2)_p$S-lower alkyl, $-(CH_2)_p$S-lower alkenyl, $-S(CH_2)_nR$, $-(CH_2)_pN(R)_2$, $-(CH_2)_p$NR-lower alkyl, $-(CH_2)_p$NR-lower alkenyl, $-NR(CH_2)_nR$, and protected forms of the above, wherein R represents, independently for each occurrence, hydrogen, or substituted or unsubstituted aryl, heterocycle, heteroaryl, alkylaryl, alkenyl, or alkyl, and wherein each occurrence of p independently represents an integer from 0-10.

8) Marked-up copy of amended claim 158:

158. A compound having the structure:

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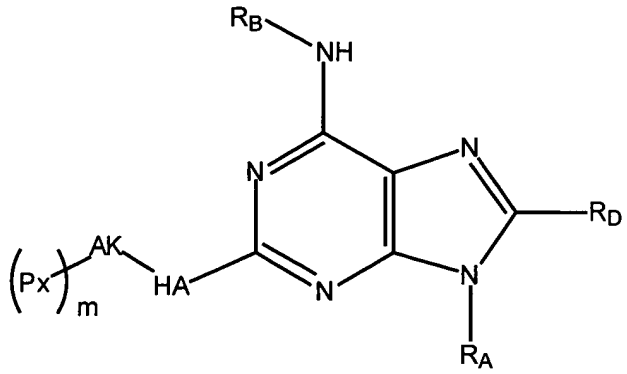

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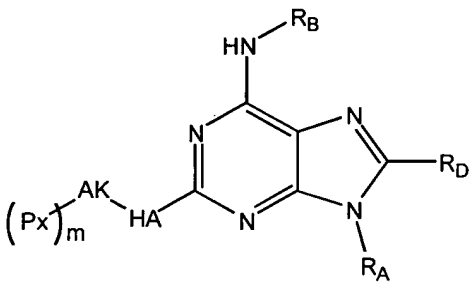
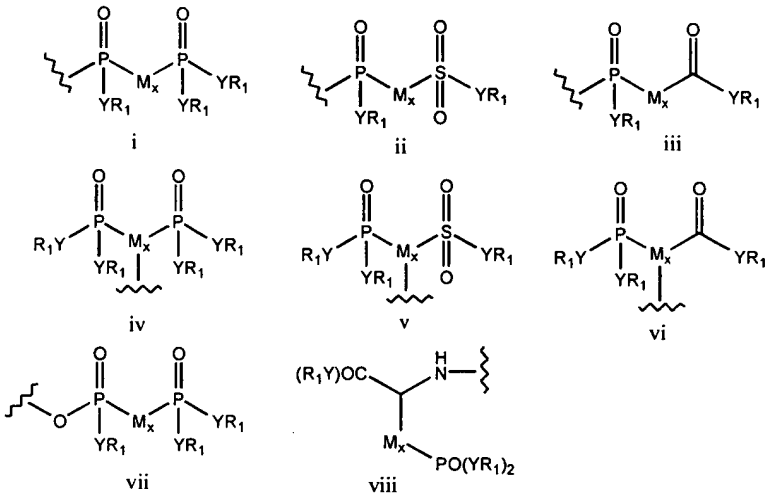


wherein R_A is hydrogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; R_B is an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; and R_D is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-ZR_E$, wherein Z is -O-, -S-, or NR_F, wherein R_E is hydrogen, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and R_F is an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein in each of the foregoing groups each aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl moiety may be branched or unbranched, cyclic or acyclic and substituted or unsubstituted, and each aryl and heteroaryl moiety may be substituted or unsubstituted; wherein AK is a linear or branched, cyclic or acyclic, substituted or unsubstituted aliphatic or heteroaliphatic moiety; and wherein HA is absent, -O-, -S- or –NH-;

wherein P_x is a phosphorus containing moiety having the structure $-P(X)YR_GYR_H$, wherein X is independently an alkyl moiety, =O or =S; R_G and R_H, for each occurrence, are independently hydrogen, or substituted or unsubstituted aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, and each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

or is a phosphorus moiety having any one of structures i-viii:



wherein each occurrence of M is independently CH_2, CHV, CHOH, or CV_2; each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl; wherein V is a halogen; each occurrence of x is independently 1-6, and in certain embodiments is 1 or 2; and each occurrence of R_1 is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, a prodrug or pharmaceutically acceptable derivative; and

wherein m is 1-3.

9) Marked-up copy of amended claim 181:

181. A method of treating or preventing bone disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the formula:

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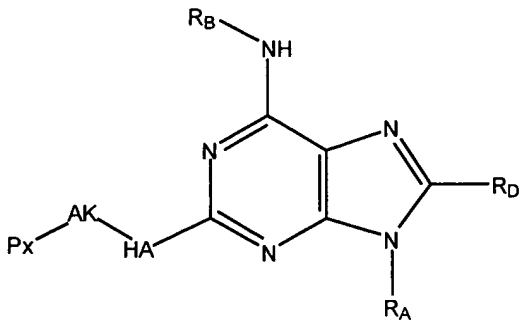

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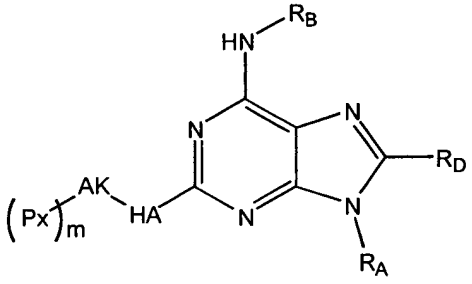
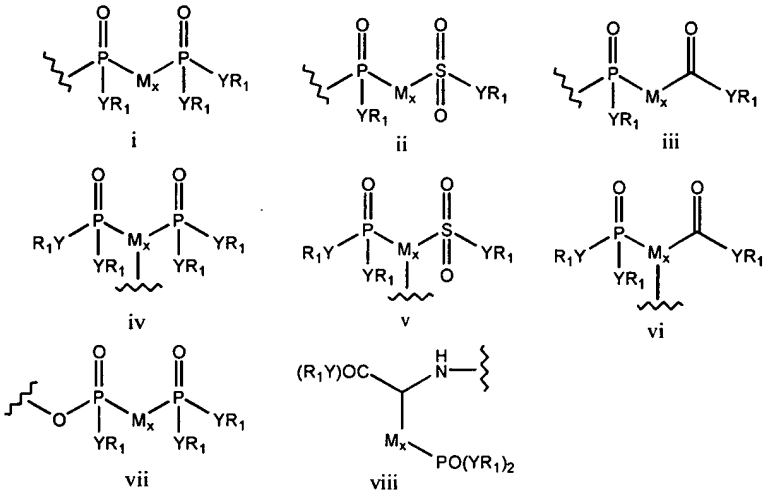


wherein R_A is hydrogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; R_B is an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety; and R_D is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-ZR_E$, wherein Z is -O-, -S-, or NR_F, wherein R_E is hydrogen, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and R_F is an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein in each of the foregoing groups each aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl moiety may be branched or unbranched, cyclic or acyclic and substituted or unsubstituted, and each aryl and heteroaryl moiety may be substituted or unsubstituted;

wherein AK is a linear or branched, cyclic or acyclic, substituted or unsubstituted aliphatic or heteroaliphatic moiety; and wherein HA is absent, -O-, -S- or –NH-;

wherein P_x is a phosphorus containing moiety having the structure $-P(X)YR_GYR_H$, wherein X is independently an alkyl moiety, =O or =S; R_G and R_H, for each occurrence, are independently hydrogen, or substituted or unsubstituted aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, and each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl;

or is a phosphorus moiety having any one of structures i-viii:



wherein each occurrence of M is independently CH_2, CHV, CHOH, or CV_2; each occurrence of Y is independently a covalent bond, -O-, -S- or $N(R_J)_2$, wherein R_J, for each occurrence, is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl; wherein V is a halogen; each occurrence of x is independently 1-6, and in certain embodiments is 1 or 2; and each occurrence of R_1 is independently hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, alkylheteroaryl, a prodrug or pharmaceutically acceptable derivative; and

wherein m is 1-3.

REMARKS

Applicants respectfully request entrance of the amendments as detailed above for the above-referenced patent application. Applicants respectfully submit that this preliminary amendment is requested 1) to correct formal matters in the specification (e.g., addition of certain priority information) or 2) to correct typographical errors. Applicants respectfully submit that no new matter is presented with these amendments. Rather, Applicants respectfully submit that support for each of the amendments, as detailed above, can be found throughout the specification and claims as originally filed.

Applicants would like to thank the Examiner in advance for review of this request. If it is believed that a telephone conversation would expedite matters, the Examiner is invited to contact the undersigned at (617) 248-5216. Although it is believed that there is no fee associated with this amendment, if Applicants are mistaken, please charge any fees to our Deposit Account No.: 03-1721.

Respectfully Submitted,

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